

# EXHIBIT C

# The Argument for Lightweight Polypropylene Mesh in Hernia Repair

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The development of polypropylene prosthetics revolutionized surgery for the repair of abdominal wall hernias. A tension-free mesh technique has drastically reduced recurrence rates for all hernias compared to tissue repairs and has made it possible to reconstruct large ventral defects that were previously irreparable. The repair of abdominal wall defects is one of the most commonly performed general surgical procedures, with over 1 million polypropylene implants inserted each year. Surprisingly, little research has been performed to investigate the interaction of abdominal wall forces on a ventral hernia repair or the required amount or strength of the foreign-body material necessary for an adequate hernia repair. The long-term consequences of implantable polypropylene prosthetics are not without concern. The body generates an intense inflammatory response to the prosthetic that results in scar plate formation, increased stiffness of the abdominal wall, and shrinkage of the biomaterial. Reducing the density of polypropylene and creating a "light weight" mesh theoretically induces less foreign-body response, results in improved abdominal wall compliance, causes less contraction or shrinkage of the mesh, and allows for better tissue incorporation. A review of the laboratory data and short-term clinical follow-up is reviewed to provide a strong basis or argument for the use of "light weight" prosthetics in hernia surgery.

*A surgeon can do more for the community by operating on hernia cases and seeing that his recurrence rate is low than he can by operating on cases of malignant disease.*

—Sir Cecil Wakely, 1948  
President  
Royal College of Surgeons

The search for an effective repair of ventral hernia has long occupied the general surgeon. Historically, tissue repairs of abdominal wall defects were met with rates of recurrence of up to 50%.<sup>1-3</sup>

The work of Dr. Francis Usher with polypropylene (Marlex) in the late 1950s revolutionized the approach to abdominal wall defects and drastically lowered the recurrence rates.<sup>4-6</sup> His experience with polyethylene provided significant advantages over the metallic meshes used at the time. Polyethylene resisted corrosion and migration inherent to tantalum and stainless steel meshes.

In 1962, the weave of the standard polypropylene mesh was changed from woven to a knitted construct. This alteration was made to prevent the ends of the mesh from unraveling when cut.<sup>7</sup> The polypropylene mesh that is used today has remained largely unchanged over the past 45 years. Polypropylene is the most commonly used prosthetic worldwide for the repair of ventral and groin hernias.

The surgical literature is replete with articles describing different mesh repair techniques for ventral and inguinal hernias and their associated rates of recurrence. Despite hernia operations being the most commonly performed procedures by general surgeons over the last 50 years, little data exist concerning the intraabdominal forces generated during normal or strenuous activity and the necessary strength of a prosthetic for repair. The standard polypropylene mesh may in fact be over-engineered or too strong. In addition, the body's reaction to these dense or "heavyweight" meshes results in intense inflammation, mesh shrinkage, and loss of abdominal wall compliance.

By reducing the amount of foreign body material, lighter-weight meshes may provide ample strength for hernia repair with less associated side effects. Second- and third-generation prosthetic biomaterials have been developed that are intentionally less dense, with less tensile strength (N/cm) than standard, nonabsorbable mesh. These bioprosthesis allow more freedom of abdominal wall motion, are more resistant to contraction because of reduced inflammation, and maintain or improve good tissue ingrowth. A strong argument for these "lightweight" meshes can be made from data concerning maximum burst strength, abdominal wall compliance, degree of foreign body response, amount of shrinkage, and advantages of larger pore sizes in the mesh.

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## Concept of Lightweight Mesh

Although the reduction in hernia recurrence rates is undeniable when a tension-free mesh repair is performed, the long-term complications of implantation of polypropylene mesh have been well documented.<sup>8</sup> The properties that serve polypropylene well for incorporation after hernia repair can also be detrimental. Polypropylene creates an intense inflammatory response that results in rapid and dense incorporation into the surrounding tissue. This excessive inflammatory reaction to heavyweight polypropylene tends to form a scar-plate around the prosthetic that results in a firm and contracted mesh. Reducing the amount of foreign body material in these meshes may reduce the inflammatory response and decrease the degree of unorganized or reactive scar formation.

Marlex (C.R. Bard, Inc, Murray Hill, NJ) is a standard monofilament heavyweight polypropylene mesh that is commonly used for hernia repair. It contains 95 g/m<sup>2</sup> of polypropylene, is porous but has very small interstices, and is extremely strong. Several comparable formulations of heavyweight polypropylene are available with a similar polypropylene content as Marlex, including Prolene (Ethicon, Inc, Somerville, NJ), Surgipro (US Surgical, Norwalk, CT), and Prolite (Atrium Medical, Hudson, NH) (Table 1).

Companies have decreased the foreign body material in their mesh by reducing the density of polypropylene filaments that compose the mesh. These bioprosthesis now fall into 3 main categories—heavyweight, mid-weight, and lightweight—according to their polypropylene content. Prolene Soft Mesh (Ethicon, Inc) contains less than half the polypropylene (45 g/m<sup>2</sup>), has larger pores, and is more compliant than heavyweight meshes. Lightweight meshes tend to have 35 g/m<sup>2</sup> of polypropylene or less. They also have very large pores, in the range of 3 to 4 mm. This reduction in prosthetic makes the mesh much softer and more flexible compared with standard meshes. An example of the available polypropylene hernia prosthetics and their densities is listed in Table 1.

As mentioned, the reduced-mass meshes are very compliant or soft. Although this increase in compliance or decrease in stiffness is an advantage to patients, the dramatic increase in flexibility of the mesh could make it difficult for surgeons to handle or manipulate it in the operating room. A certain stiffness, or ability of the mesh to hold its shape, eases placement of the prosthetic inside or outside the abdomen.

In an effort to improve handling characteristics of these lightweight meshes, manufacturers incorporated absorbable filaments into the weave of the mesh. These absorbable components add stiffness during implantation but then readily absorb. Vypro (Ethicon, Inc) was the first lightweight partially absorbable mesh. It contains lightweight polypropylene interwoven with multifilamented polyglactin 910 (Vicryl, Ethicon, Inc). The Vicryl component begins to dissolve immediately and is microscopically absent in 60 to 90 days.

Because the multifilamented nature of the Vicryl in Vypro may contribute to increased surface area and potentially a higher infection risk, the next generation product included a partially absorbable monofilament woven within polypropylene. Ultrapro (Ethicon, Inc) is a recently introduced mesh that is composed of a weave of lightweight polypropylene and poliglecaprone, the same material that is in Monocryl (Ethicon, Inc) suture (Figure 1). The poliglecaprone, which is a mono-filament, gives the mesh added stiffness for handling and dissolves in approximately 90 days.

## Burst Strength

Calculations of intraabdominal pressure and compliance of the abdominal wall have called into question the need for heavyweight polypropylene. Schumpelick and colleagues<sup>9</sup> have attempted to study the elasticity and tensile strength of the abdominal wall. Calculations based on Pascal's principle of hydrostatics have predicted the maximum

**Table 1.** Polypropylene meshes of differing densities

Surgipro <sup>a</sup>	110 g/m <sup>2</sup>
Prolene <sup>b</sup>	105 g/m <sup>2</sup>
Marlex <sup>c</sup>	95 g/m <sup>2</sup>
Prolite <sup>d</sup>	90 g/m <sup>2</sup>
Prolene Soft Mesh <sup>b</sup>	45 g/m <sup>2</sup>
Vypro II <sup>b</sup>	35 g/m <sup>2</sup>
Ultrapro <sup>b</sup>	28 g/m <sup>2</sup>

<sup>a</sup>United States Surgical, Norwalk, CT

<sup>b</sup>Ethicon, Inc, Somerville, NJ

<sup>c</sup>CR Bard, Inc, Cranston, RI

<sup>d</sup>Atrium Medical Co, Hudson, NH

rensile strength of the abdominal wall to be 16 N/cm.<sup>10</sup> Standard heavyweight polypropylene mesh has been shown to have a bursting strength that is 6 to 10 times this calculated force. From their mathematical models and stereotaxy of the human abdomen, it can be hypothesized that the currently available prosthetics are, in fact, too strong, more dense, and less compliant than needed for an optimal hernia repair.<sup>10</sup> However, the abdominal wall pressures in their models are calculated and not a direct measure.

The initial fixation strength of the various surgical techniques and the tissue overlap of the prosthetic are the principal factors in the early success of a mesh hernia repair. Suture or metallic attachment devices must resist maximum intraabdominal pressures, forces of wound contraction, and potential mesh migration.

The long-term success of the repair ultimately depends on the fibrocollagenous ingrowth of the tissue into the mesh. How strong a biomaterial needs to be and the required amount of incorporation of the mesh into the patient's tissues have yet to be determined. In fact, the normal intraabdominal forces prosthetic biomaterials encounter *in vivo* had not been truly and accurately measured in a quantita-

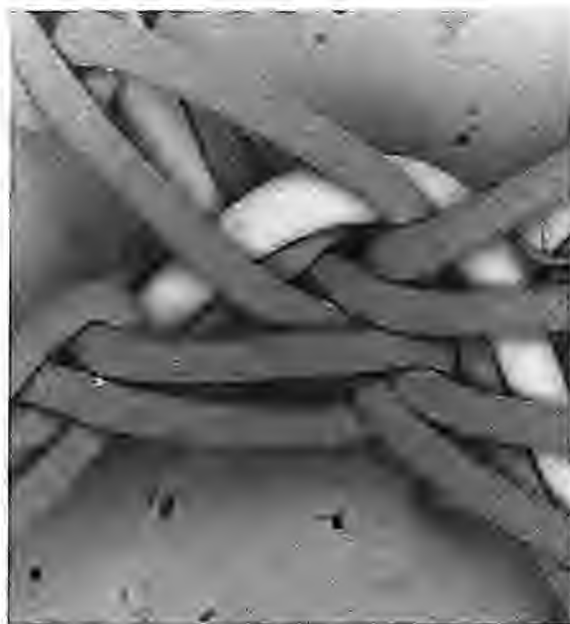
tive manner. Previous cadaveric models have predicted that the maximum, instantaneous force generated in the abdomen to be about 150 mm Hg<sup>11</sup>; however, the forces acting on the abdomen during everyday activities were relatively unknown.

To answer this question, we measured the ranges of maximum intraabdominal pressures (IAP) via bladder catheters in young adults during routine activities.<sup>12</sup> The maximum intraabdominal pressures generated by healthy, non-obese individuals in our study occurred during coughing and jumping. While coughing, the maximum intraabdominal pressures were 127 mm Hg while sitting and 141 mm Hg standing. A pressure as high as 252 mm Hg was obtained while a test subject jumped in place. For Valsalva in this healthy adult population, the maximum pressures were 64 mm Hg while sitting and 116 mm Hg standing.

Considering the abdominal cavity as a cylinder and using Pascal's principle of hydrostatics, the maximum tensile strengths would range from 11 N/cm to 27 N/cm for these exercises. Biomaterials and their fixation should tolerate these pressures to minimize the risk of hernia recurrence. Klinge et al<sup>11,13</sup> demonstrated that the heavyweight polypropylene currently in use tolerates rupture forces of up to 100 N/cm.

We used a porcine model to evaluate the biomechanical properties of heavyweight (Marlex), mid-weight (Prolene Soft Mesh), and lightweight (Ultrapro) polypropylene mesh after 5 months of implantation.<sup>14</sup> The burst strengths for all meshes in this study were highly supraphysiologic. The burst load for the native abdominal wall fascia averaged 232 N. The mean burst loads for the lightweight (576 N) and mid-weight (590 N) meshes were more than twice this. The heavyweight mesh demonstrated excessive burst loads of greater than 1200 N. These burst strengths far exceed the normal forces acting on the abdominal wall fascia both before implantation and after 5 months within the abdomen.

Recurrences of abdominal wall hernia repairs are rarely due to failure of the mesh itself. Indeed, there is only a single report<sup>15</sup> of central mesh failure with a heavyweight polypropylene mesh. Rather than surmising that the mesh was too weak, the authors postulated that the increased stiffness of the heavyweight mesh at its interface with the compliant abdominal wall resulted in damage to the mesh or a fracture that caused its failure over years.<sup>15</sup> Failure of hernia repairs nearly always occurs laterally at the mesh-tissue interface because of a failure of fixation, incorporation, or lack of overlap.



**Figure 1.** Electron micrograph at  $\times 60$  magnification demonstrating the weave of Ultrapro partially absorbable mesh. The poliglecaprone (Monocryl) appears white and is interwoven with two strands of lightweight polypropylene.

## Abdominal Wall Compliance

There are consequences to the long-term implantation of polypropylene. As previously mentioned, heavyweight meshes elicit an intense inflammatory response that produces a scar plate or thick capsule around the mesh (Figure 2) and results in reduced compliance of the abdominal wall.<sup>16</sup> This was well demonstrated by ultrasound examination and 3D stereography in patients having undergone ventral hernia repair with both heavyweight and lightweight meshes.<sup>17</sup> All meshes showed an increased stiffness of the abdominal wall with reduced height and diminished curvature at maximum abdominal distention. The extent of stiffness significantly increased in direct proportion to mesh weight and was inversely related to pore size, that is, a larger pore size yielded a more compliant or softer mesh *in situ*.

The curvature of the abdominal wall increased over time with the lightweight mesh, which was not seen with any of the heavyweight meshes.<sup>17</sup> When heavyweight polypropylene meshes were removed from human subjects during reoperations, Klinge and colleagues microscopically confirmed what had been seen in animal experiments: the inflammatory process at the mesh-tissue interface demonstrated pronounced perifilamentous fibrosis and deposition of unorganized collagen fibers. The entire polypropylene mesh was encapsulated by connective tissue that formed a rigid scar plate.<sup>18</sup> This phenomenon is believed to contribute to increased stiffness of the mesh and abdominal wall.

In our *in vivo* study mentioned previously, the mid-weight and lightweight meshes demonstrated significant reduction in stiffness as the absorbable component dissolved compared with the heavyweight mesh. Following explantation, the lightweight mesh was significantly more compliant or least stiff. However, before implantation, the absorbable Monocryl (poliglecaprone) component makes the lightweight mesh the stiffest of all the meshes (68.6 N/cm).

As previously stated, the purpose of the poliglecaprone interwoven with the thin polypropylene is to increase stiffness to improve handling during implantation. However, the improvement in compliance demonstrated after degradation of the poliglecaprone much more closely approximates the physiology of the abdominal wall. We are currently prospectively following patients after the implantation of lightweight mesh for large ventral hernia defects. The endpoints of this study will include patient comfort, abdominal wall compliance, complications, and recurrence.

## Foreign Body Response

The most important factor influencing the biocompatibility or tolerance of a subject to a foreign body is the intensity and extent of inflammation and the wound healing associated with the material. The degree of inflammatory reaction to a biomaterial affects its incorporation into the implant site. The formation of connective tissue correlates well with the degree of inflammation. Moreover, the extent of the foreign body reaction to mesh prosthetics depends on the amount of the incorporated material.<sup>19</sup>

The increased ingrowth of connective tissue when associated with inflammatory or giant cells does not necessarily translate into strength and durability after hernia repair. Lightweight mesh with reduced polypropylene density and larger pore sizes between filaments has shown a pronounced reduction in inflammation and improved integration into surrounding tissue in humans.<sup>18</sup>

Histologically, in a long-term study in a pig model, we observed more scar plate or capsule formation with heavyweight mesh compared with lightweight mesh (Figure 2).<sup>20</sup> The number of inflammatory cells was statistically less in the lightweight mesh (Figure 3). As a result, the degree of overall tissue incorporation was substantially better with lightweight mesh compared with its heavyweight counterpart.

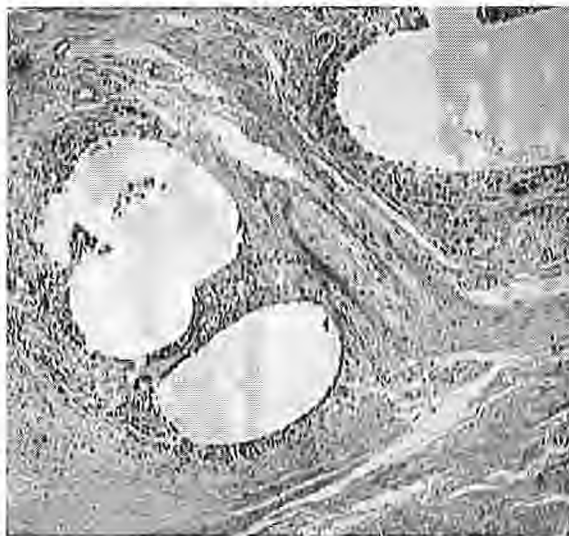
In a rat model of ventral hernia repair, Klinge et al<sup>21</sup> demonstrated that biomaterials with a larger pore size and decreased polypropylene content exhibited a reduction in inflammation and fibrosis with microscopic attributes of normal healing tissue compared with more dense polypropylene-containing materials. At the cellular level, measurements of apoptosis and proliferation were elevated in the heavyweight mesh groups, implying an increased amount of cellular turnover. The lightweight mesh appears to demonstrate more physiologic levels of turnover.

The foreign-body reaction to nonabsorbable meshes was studied by histologically examining explanted mesh specimens removed during revision operations.<sup>18</sup> The investigators found that permanent heavyweight meshes cause a persistent inflammatory reaction at the mesh-tissue interface for months to years after implantation. The host adapts to the "inert" foreign body to a degree, and then encases the mesh in a surrounding collagen capsule to protect the host tissues.<sup>18</sup> The persistence of this foreign-body reaction is important, especially in young patients in whom the mesh will remain for several decades.

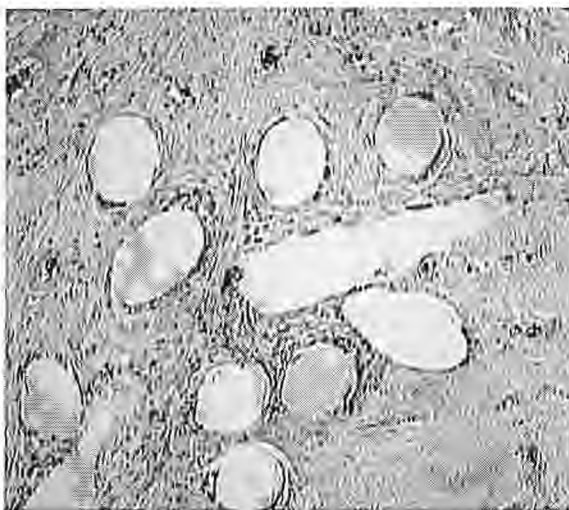
Clinically, the reduction in foreign-body reaction translates into theoretically fewer complaints of paraesthesias and functional complaints. Welty et al<sup>17</sup> demonstrated the superiority of lightweight polypropylene mesh biomaterials for incisional hernia repairs.<sup>17</sup> More complaints were seen in patients younger than 50 years of age. In the heavyweight Marlex group, 58% had complaints of paresthesia compared with only 4% in the lightweight Vypro group.<sup>17</sup>

### Degree of Shrinkage

One concern with the long-term implantation of mesh is the amount of shrinkage or passive compression the material undergoes. All available meshes, regardless of their composition, experience a 20% to 50% reduction in their initial size. Factors of the mesh itself and the surrounding tissue inflammatory response contribute to this phenomenon. The reality of mesh contraction, whatever the

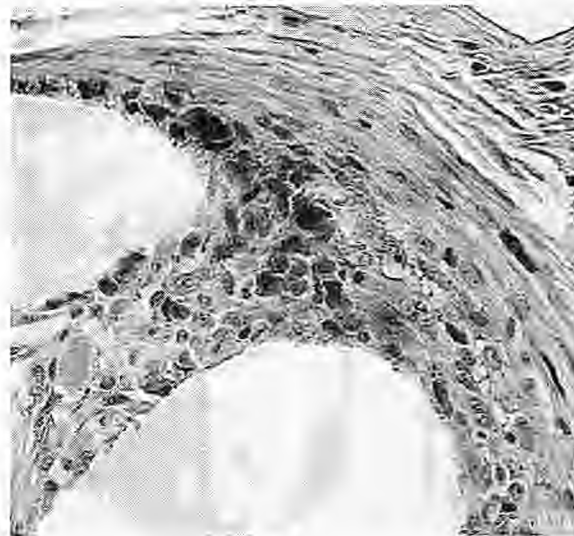


A

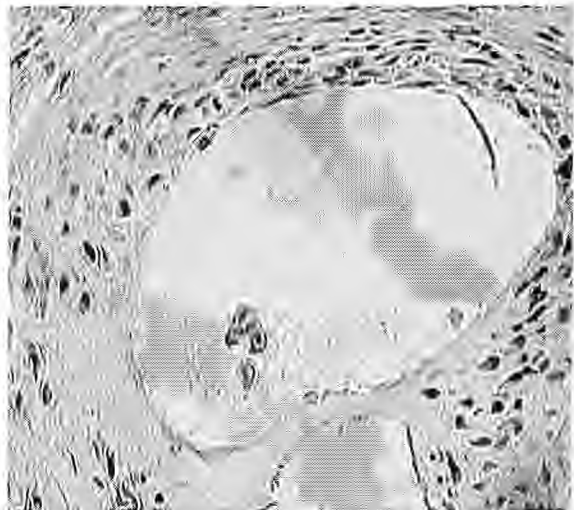


B

**Figure 2. (A)** Heavyweight mesh ( $\times 40$ , Trichrome stain) induces a thick scar around the mesh with bridging fibrosis or unorganized collagen between the filaments. **(B)** Lightweight mesh ( $\times 40$ , Trichrome stain) demonstrates better tissue incorporation with less scar plate formation.



A



B

**Figure 3. (A)** Tissue response 5 months after heavy weight mesh implantation ( $\times 400$ , Trichrome stain) demonstrates abundant inflammatory, giant cells. **(B)** The lightweight mesh ( $\times 400$ , Trichrome stain) produces much less inflammation, with more stromal cells and fibroblasts.

reason, strongly supports the concept of wide tissue overlap, which has been long advocated by proponents of the retro-rectus repair and, more recently, the laparoscopic repair.<sup>22</sup>

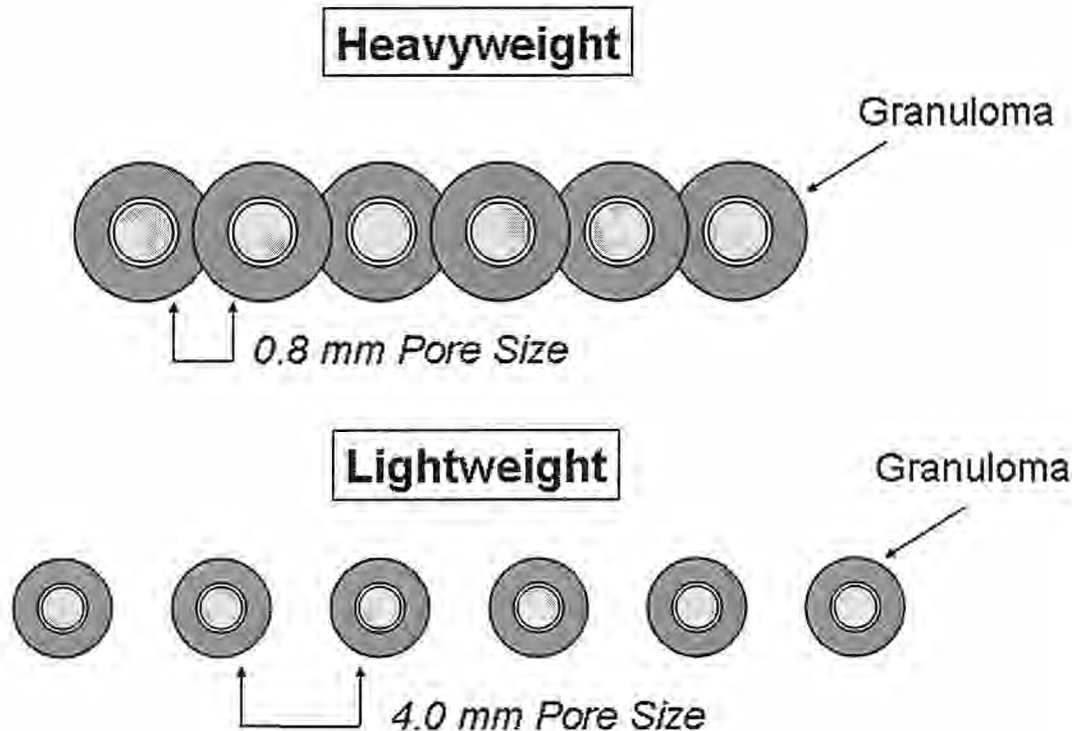
In a dog model, the shrinkage of heavyweight polypropylene mesh and a lightweight polypropylene mesh with absorbable polyglactin 910 were compared. It demonstrated that all polypropylene meshes shrink 30% to 50% of their original size within 2 to 6 months after implantation. The lightweight mesh showed less inflammatory response and reduced shrinkage (34% vs 46%).<sup>23</sup>

Initially, macrophages are an important cell population associated with the inflammatory reaction to biomaterials. The absorbable fraction of lightweight polypropylene mesh may be responsible for high macrophage counts at day 7 and a pronounced reduction of the macrophage index after 90 days.<sup>19</sup> The presence of the absorbable poligle-caprone in Ultrapro mesh may initially create an inflammatory reaction that resolves as this portion of the prosthetic absorbs. Over a longer period of time, this effect may diminish and result in less passive compression of the lightweight mesh.

### Increased Pore Size

The pore size of prosthetic mesh has an important effect on the biocompatibility of the foreign body after implantation. An in vivo study after implantation of heavyweight mesh and an experimental lightweight polypropylene mesh demonstrated a significant increase of total and mature type I collagen deposition with the lightweight mesh containing larger pores. The tensile strength of the large-pore mesh increased after 30-day implantation in the dog, whereas it remained the same for the smaller-pore heavyweight mesh.<sup>24</sup>

A similar study evaluated heavyweight, small-pore Marlex mesh and lightweight, large-pore Vypro mesh with an absorbable component. The large-pore mesh was integrated in a loose network of perifilamentous fibrosis with fat tissue present in between. In contrast, the small-pore mesh was incorporated entirely in perifilamentary granulomas and scar tissue, which bridged the whole pore diameter of less than 1 mm.<sup>21</sup> It appears that the greater distance between pores resists the ability of "bridging fibrosis" (Figure 4), contributing to im-



**Figure 4.** Small pores of heavyweight polypropylene allow for intense peri-filamentous fibrosis with bridging to adjacent filaments. Macroporous meshes that have less polypropylene incite less of a foreign body reaction with less bridging fibrosis.

proved compliance and theoretically less passive compression of the biomaterial.

## Conclusion

The use of a polyethylene polymer in a mesh configuration has changed the face of hernia surgery over the past 50 years. The techniques describing the precise method of placement of this mesh are exhausting, and recurrence rates have reached a nadir with the currently available mesh. The continued search for the ideal hernia repair with reduced long-term morbidity will shift away from discussing the type of repair and turn to an evaluation of the type of mesh used in the repair.

The implantation of a macroporous, lightweight polypropylene mesh results in less restriction of abdominal wall compliance while providing more than adequate strength for the repair of ventral hernias. These new class of meshes for abdominal wall hernia repair are lightweight, or more correctly termed, *physiologic-weight* materials. Continued, prospective evaluations of various polypropylene mesh formulations in the clinical setting are required for a more thorough assessment of the role of these promising bioprosthesis in the repair of ventral hernias, and, as well, will determine "how low we can go" with the amount of foreign body material.

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